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Review

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Low-density lipoprotein size and cardiovascular risk assessment

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Summary

A predominance of small, dense low-density lipoproteins (LDL) has been accepted as an emerging cardiovascular risk factor by the National Cholesterol Education Program Adult Treatment Panel III. LDL size seems to be an important predictor of cardiovascular events and progression of coronary heart disease and evidences suggests that both quality (particularly small, dense LDL) and quantity may increase cardiovascular risk. However, other authors have suggested that LDL size measurement does not add information beyond that obtained by measuring LDL concentration, triglyceride levels and HDL concentrations. Therefore, it remains debatable whether to measure LDL particle size in cardiovascular risk assessment and, if so, in which categories of patient. Therapeutic modulation of LDL particle size or number appears beneficial in reducing the risk of cardiovascular events, but no clear causal relationship has been shown, because of confounding factors, including lipid and non-lipid variables. Studies are needed to investigate the clinical significance of LDL size measurements in patients with coronary and non-coronary forms of atherosclerosis; in particular, to test whether LDL size is associated with even higher vascular risk, and whether LDL size modification may contribute to secondary prevention in such patients.

Introduction

Cardiovascular diseases are still the primary cause of death in most industrialized countries. Effective prevention includes treatment of a series of risk factors: smoking, hypertension, diabetes, obesity, and dyslipidaemia, which includes elevated triglycerides, total and low-density-lipoprotein (LDL) cholesterol levels, as well as lowered high-density-lipoprotein (HDL) cholesterol.[1]

The therapeutic modulation of distinct LDL subspecies is also of great benefit in reducing the risk of cardiovascular events.[1–3] The peak size of LDL in humans shows a bimodal (rather than a normal) distribution, and can be separated into two phenotypes that differ in size, density, physico-chemical composition, metabolic behaviour and atherogenicity. These phenotypes have been called 'pattern A' (larger, more buoyant LDL) and 'pattern B' (smaller, denser LDL predominate).[2–5]

LDL size correlates positively with plasma HDL levels and negatively with plasma triglyceride concentrations, and the combination of small, dense LDL, decreased HDL cholesterol and increased

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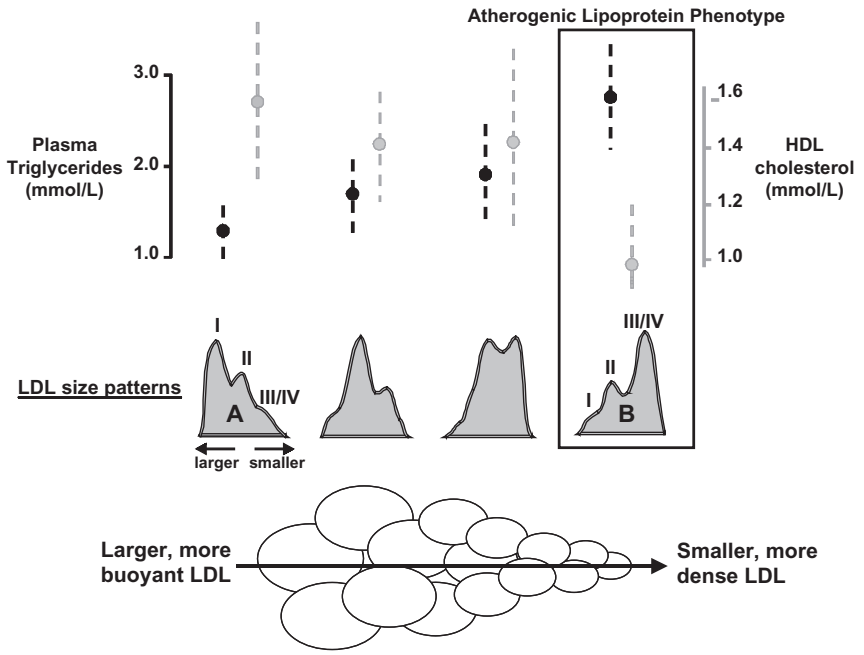

Figure 1. LDL heterogeneity and plasma triglyceride and HDL cholesterol concentrations (modified from reference 3).

triglycerides has been called the 'atherogenic lipoprotein phenotype'[6] (Figure 1). This partly heritable trait is a feature of the metabolic syndrome, and is associated with increased cardiovascular risk.

LDL size seems to be an important predictor of cardiovascular events and progression of coronary artery disease, and a predominance of small, dense LDL has been accepted as an emerging cardiovascular risk factor by the National Cholesterol Education Program Adult Treatment Panel III.[1] However, other authors have suggested that LDL subclass measurement does not add independent information to that conferred by the simple LDL concentration, along with the other standard risk factors.[7] Thus it remains debatable whether to measure LDL particle size for cardiovascular risk assessment, and if so, in which categories of patients.

LDL size and environmental/genetic influence

The prevalence of the pattern B phenotype is approximately 30% in adult men, 5–10% in young men and women <20 years, and approximately 15–25% in post-menopausal women.[2,3] LDL size is genetically influenced, with a heritability ranging from 35–45%, based on an autosomal dominant or codominant model with varying additive and polygenic effects.[8] Clearly, non-genetic and environmental factors influence the expression of this phenotype, and abdominal adiposity and oral contraceptive use are both associated with an increase in small, dense LDL.[9–11]

Dietary factors are also important. A very low-fat high-carbohydrate diet can induce pattern B in people who are genetically predisposed to this phenotype.[12] In addition, the predominance of small, dense LDL is commonly found in conjunction with familial disorders of lipoprotein metabolism that are associated with increased risk of premature coronary artery disease, including familial combined hyperlipidaemia, hyper-beta-lipoproteinaemia and hypo-alpha-lipoproteinaemia.[2]

LDL size measurement

Particle size distribution of plasma LDL subfractions may be measured by different laboratory techniques,[7] but the most common procedure is 2–16% gradient gel electrophoresis at 10°C using a Tris (0.09 M)-boric acid (0.08 M)-Na_2EDTA (0.003 M) buffer (pH 8.3).[9,13] Plasma is adjusted to 20% sucrose, and 3–10 µl are applied to the gel. Potentials are set at 40 mV (15 min), 80 mV (15 min), and 125 mV (24 h). Gels are fixed and stained for lipids in a solution containing oil red O in 60% ethanol at 55°C, and for proteins in a solution containing 0.1% Coomassie brilliant blue R-250, 50% ethanol and 9% acetic acid, and then

scanned with a densitometer. Molecular diameters are determined on the basis of migration distance, by comparison with standards of known diameter.[9,13]

Assignment of LDL subclass phenotypes is based on the particle diameter of the major plasma LDL peak. LDL phenotype A (larger, more buoyant LDL) is defined as an LDL subclass pattern with the major peak at a particle diameter of 258 Å or greater, whereas the major peak of LDL phenotype B (small, dense LDL) is at a particle diameter of <258 Å[2,3,9,14] (Figures 2 and 3).

Atherogenicity of small, dense LDL

Several reasons have been suggested for the atherogenicity of small, dense LDL. Smaller, denser LDL are more easily taken up by arterial tissue than are larger LDL,[15] suggesting greater transendothelial transport of smaller particles. In addition, smaller LDL particles may also have decreased receptor-mediated uptake and increased proteoglycan binding.[16] Sialic acid, perhaps because of its exposure at the LDL surface, plays a determinant role in the *in vitro* association of LDL with the polyanionic proteoglycans,[17] and the sialic acid content of LDL particles is lower in subjects with the pattern B phenotype.

Oxidative susceptibility increases and antioxidant concentrations decrease with decreasing LDL size.[18] The altered properties of the surface lipid layer associated with a reduced content of free cholesterol[19] and increased content of polyunsaturated fatty acids[20] might also contribute to the enhanced oxidative susceptibility of small, dense LDL.

Recently,[21] we chose apoB transgenic mice to evaluate the kinetic behaviour of human LDL particles of different size *in vivo* in a genetically homogeneous recipient, thus avoiding other metabolic differences that could influence LDL metabolism. We found that small LDL particles had intrinsic features that led to retarded metabolism and decreased intra/extravascular equilibration compared to medium-sized LDL; these properties could contribute to the greater atherogenicity of small, dense LDL.

Association of LDL size with cardiovascular events and disease progression

The magnitude and independence of the association of LDL size with cardiovascular diseases has been tested in many studies, including cross-sectional and prospective epidemiological studies, as well as clinical intervention trials.[22–72] (Table 1). The vast majority (but not all) show a significant univariate association of small, dense LDL with increased coronary heart disease (CHD) risk. However, LDL size is seldom a significant and independent predictor of CHD risk after multivariate adjustment for confounding variables, in particular plasma triglyceride levels and HDL cholesterol concentrations (Table 1).

Therefore, it may be that the increased risk associated with smaller LDL size in univariate analyses is a consequence of the broader pathophysiology of which small, dense LDL is a part (e.g. high triglycerides, low HDL cholesterol, increased LDL particle number, obesity, insulin resistance, diabetes, metabolic syndrome), rather than a reflection of an intrinsic increased atherogenic potential. A clear causal relationship between small dense LDL and increased cardiovascular risk cannot be proven, based on our present knowledge.

This is further complicated by the fact that at the same level of LDL cholesterol, higher-risk pattern B individuals have significantly more particles than those with pattern A. The number of LDL particles in plasma is potentially important, because the arterial walls are exposed to these particles, and an increased number might increase atherogenicity independently of particle size.[73] Is the higher risk of pattern B individuals attributable to the fact that they have more LDL particles in total, or does the smaller size contribute independently to CHD risk?

Assessment of LDL particle size by gradient gel electrophoresis does not provide information about the concentration or number of small, dense LDL particles, which has been historically estimated by measuring apo B concentrations.[74] Rader[75] and Sniderman[76] reviewed 32 trials that studied the relationship between plasma apo B concentrations and CHD risk, but the data did not consistently support a stronger association between CHD risk and apo B then between CHD and other lipid parameters.

LDL particle number is currently assessed by nuclear magnetic resonance, which provides data on both LDL particle size and concentration.[77] Higher LDL particle concentrations seem to be important in determining CHD risk,[78,79] but few studies have assessed whether the quantity rather than the size of small, dense LDL is more strongly associated with CHD risk.[55–57,72] In these studies, the number of total and smaller LDL particles was a significant and independent predictor of CHD risk, after multivariate adjustment for lipid variables[55–57,72] (Table 1).

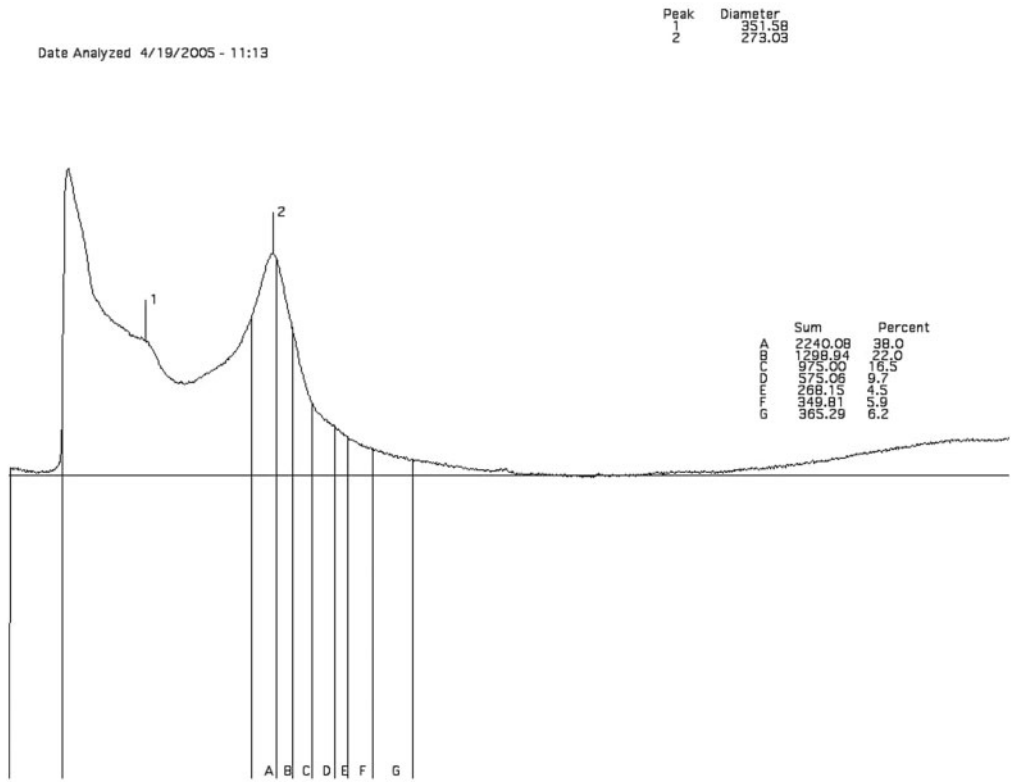

Figure 2. Densitometric scan of lipid-stained 2–16% non-denaturing gradient gel electrophoresis of whole plasma from a subject with a predominance of large, buoyant LDL (LDL phenotype 'pattern A').

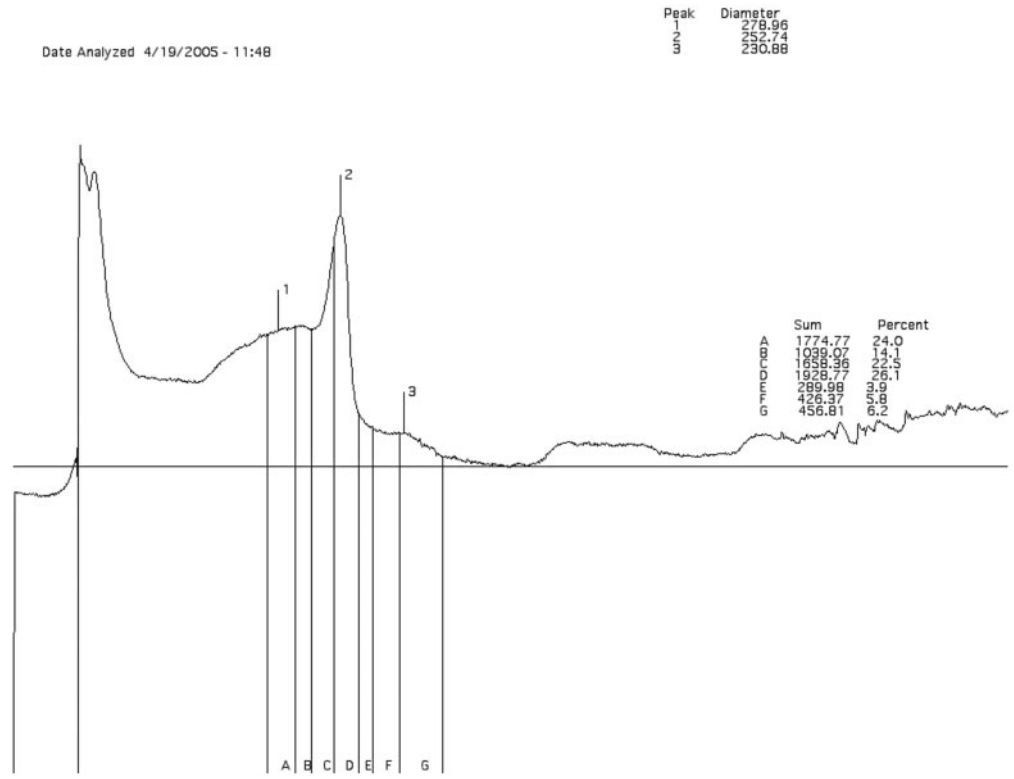

Figure 3. Densitometric scan of lipid-stained 2–16% nondenaturing gradient gel electrophoresis of whole plasma from a subject with a predominance of small, dense LDL (LDL phenotype 'pattern B').

Table 1 Univariate and multivariate analyses on the association of size or number of small, dense LDL particles with cardiovascular diseases

Author	Study design	Univariate	Multivariate	Author	Study design	Univariate	Multivariate
LDL size							
Crouse[22]	CS	Y	N	Skoglund[47]	CS	Y	Y
Austin[23]	CS	Y	N	Zambon[48]	P	Y	Y
Griffin[24]	CS	Y	N	Austin[49]	P	Y	N
Tornvall[25]	CS	Y	–	Hulthe[50]	CS	N	–
Campos[26]	CS	Y	N	Hulthe[51]	CS	Y	–
Coresh[27]	CS	Y	N	Bokemark[52]	CS	Y	N
Griffin[28]	CS	Y	Y	Campos[53]	P	N	N
Campos[29]	CS	N	N	Kamigaki[54]	CS	Y	N
Sherrard[30]	CS	N	–	Rosenson[55]	P	Y	Y
Rajman[31]	CS	N	–	Blake[56]	P	Y	N
Stampfer[32]	P	Y	N	Kuller[57]	P	Y	N
Gardner[33]	P	Y	Y	Liu[58]	CS	Y	Y
Miller[34]	P	Y	N	Koba[59]	CS	Y	Y
Mack[35]	P	Y	N	Vakkilainen[60]	P	Y	N
Lamarche[36]	P	Y	Y	Slowik[61]	CS	Y	–
Gray[37]	CS	N	–	Hallman[62]	CS	Y	–
Wahi[38]	CS	N	–	Watanabe[63]	CS	Y	–
Slyper[39]	CS	N	–	Wallenfeldt[64]	P	Y	–
Freedman[40]	CS	Y	N	Kullo[65]	CS	Y	N
Ruotolo[41]	P	Y	N	van Tits[66]	P	Y	–
O'Neal[42]	CS	Y	Y	Inukai[67]	CS	Y	Y
Landray[43]	CS	Y	N	Mohan[68]	CS	Y	–
Hulthe[44]	CS	Y	–	Yoon[69]	CS	Y	Y
Mykkanen[45]	P	N	N	St Pierre[70]	P	Y	–
Erbey[46]	CS	Y	N	Berneis[71]	CS	Y	Y
LDL number							
Rosenson[55]	P	Y	Y	Kuller[57]	P	Y	Y
Blake[56]	P	Y	Y	Otvos[72]	P	Y	Y

CS, cross-sectional; P, prospective; Y, yes; N, no.

In addition, studies that measured not only LDL cholesterol concentration and particle size, but also LDL particle numbers in plasma, have provided important information on the risk of CHD.[73,77] When both number of LDL particles and LDL size are measured in the same study population, small, dense LDL particles are frequently not significantly associated with CHD risk.[34,36,41,56,57] (Table 1).

These data underline the clinical importance of assessing LDL particle number in establishing the risk of CHD associated with the presence of small, dense LDL particles.[74,77]

LDL size and acute myocardial infarction

Acute myocardial infarction and the atherogenic lipoprotein phenotype seem to share a similar array of interrelated metabolic aberrations, including modifications in plasma lipids and lipoproteins as well as a relative resistance to insulin-mediated glucose uptake. The common lipid alterations observed during the acute phase of myocardial infarction include a rise in triglyceride levels and a fall in total, LDL and HDL cholesterol concentrations[80–82] and such modifications have a great clinical relevance, since they must be taken into account in making therapeutic decisions.[83]

However, despite the data regarding modifications of total plasma lipoprotein fractions during a myocardial infarction, it is less certain whether LDL peak particle size is also modified in the acute phase, and therefore what the best time is to measure it. In a group patients admitted to hospital for a myocardial infarction, and followed until discharge and 3 months after the event, reduction of LDL peak particle size was premature and persisted during the hospitalization, with a significant increase 3 months after the myocardial infarction.[84] In addition, the timing of these changes seemed to precede those of all other lipoproteins.

Even angina itself (against a background of coronary artery spasm), without atherosclerosis, may lower LDL size.[85]

LDL size and vascular disease

According to the National Cholesterol Education Program Adult Treatment Panel III, clinical forms of non-coronary atherosclerosis carry a risk for CHD equal to those with established CHD.[1] These conditions include peripheral arterial disease, symptomatic (transient ischaemic attack or stroke of carotid origin) and asymptomatic (>50% stenosis on angiography or ultrasound) carotid artery disease and abdominal aortic aneurysm.[1]

However, despite plentiful data on the relationship between LDL size and atherosclerosis in patients with CHD, very few authors have investigated such relationships in patients with non-coronary forms of atherosclerosis, and studies with larger number of patients are needed. But the available data suggest a strong association between small, dense LDL and non-coronary forms of atherosclerosis.

Smaller, denser LDL particles are a risk factor for peripheral arterial disease, whether in the absence or presence of diabetes.[42] In some studies, common features of peripheral arterial disease are represented by increased triglyceride levels and lower HDL cholesterol concentrations,[42] and patients with such lipid abnormalities mostly have atherogenic small, dense LDL particles.[6,86]

The association between carotid disease and small, dense LDL has been found in healthy subjects[43,47,51,52,62] as well as in various categories of patients (familial combined hyperlipidemia, familial hypercholesterolemia, vascular dementia, Alzheimer's disease, insulin resistance or type 2 diabetes).[44,58,63,66,71] It has also been recently suggested that carotid atherosclerosis regression or progression may be linked to LDL size.[64,66]

No published studies have directly examined the association of LDL size with the presence of abdominal aortic aneurysms. However, patients with abdominal aortic aneurysms show an elevated prevalence of the metabolic syndrome,[87] which is associated with the predominance of small, dense LDL,[2,3,6] and therefore such patients are likely to have reduced LDL size.

Clinical value of therapeutic modification of LDL size

Hypolipidaemic treatment can alter LDL subclass distribution, and statins and fibrates are currently the most widely used lipid-lowering agents. Statins are potent inhibitors of hydroxy-methyl-glutaryl-coenzyme A reductase, the rate-limiting enzyme in hepatic cholesterol synthesis, and are the primary drugs of choice for the treatment of elevated plasma LDL cholesterol concentrations.[74] Fibrates have a major impact on triglyceride metabolism, mediated by peroxisomal proliferation activator receptors (PPAR) and through stimulation of lipoprotein lipase.[88]

Statins potentially lower large, medium and small LDL particles, but with wide variation between the different agents. Treatment with pravastatin favourably altered LDL size in four studies,[89–92] but not in others.[93–104] Similarly, simvastatin therapy showed significant,[105–110] moderate[111,112] or no effect[113–124] on LDL subclasses. Fluvastatin and atorvastatin seem to be more effective: fluvastatin favourably altered LDL size in six studies,[125–130] but not in two; [131,132] treatment with atorvastatin was more often beneficial[104,109,133–148] than not.[124,149–158] Promising data were also recently published on the use of rosuvastatin.[159]

Fibrates seem to have more effect than statins on LDL size. Therapy with fenofibrate, bezafibrate and gemfibrozil usually results in a beneficial effect,[100,101,107,109,117,118,145,149,151,160–176] with very rare negative findings.[113,177]

As already reported,[88] although not directly demonstrated, modulation of LDL size with fibrates probably contributed to the reduction of CHD risk in the Helsinki Heart Study and in the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trials Study Group.[178–180] It is also likely that there was a bias towards small LDL in clinical trials that showed cardiovascular benefit from statins.[181–183]

Other studies have investigated whether therapeutic modification of LDL particle size and number reduces cardiovascular risk, using arteriographic changes as outcome variables. CAD progression in the controls is significantly greater in patients with a predominance of small, dense LDL,[35,184] and arteriographic benefit is concentrated in patients with a predominance of small, dense LDL who receive treatment that tends to lower it. These studies included the Stanford Coronary Risk Intervention Project, the Familial Atherosclerosis Treatment Study (FATS), the St Thomas' Atherosclerosis Regression Study (STARS) and the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial.[34,48,55,185]

In all of these studies, therapeutic modulation of LDL size was significantly associated with reduced CHD risk on univariate analysis. Under multivariate analysis with adjustments for confounding factors,

changes in LDL size by drug therapy were the best correlates of changes in coronary stenosis in FATS,[48] and the smallest LDL fraction was the plasma lipoprotein subfraction with the single most powerful effect on CAD regression in middle-aged men with hypercholesterolaemia in STARS.[185]

In PLAC-I, using a logistic regression models that adjusted for lipid levels and other confounding factors, elevated levels of small LDL were associated with a nine-fold increased risk of CAD progression, but only in the placebo group.[55] In addition, in this study, elevated LDL particle number was a predictor of CAD progression after adjustment for race, sex, age, treatment group, baseline lumen diameter and plasma lipids.[55]

All these data suggest that the therapeutic modification of LDL size, or number of small LDL particles, is significantly associated with reduced cardiovascular risk, even after multivariate adjustment for confounding factors. However, whether LDL size or number of LDL particles is more (or equally) important can not be concluded from the current evidence.

Conclusions

Genetic and environmental factors influence the expression of small, dense LDL, which is not completely independent of traditional lipids, correlating negatively with plasma HDL concentrations and positively with plasma triglyceride levels. Small, dense LDL are associated with the metabolic syndrome, and with increased risk for cardiovascular disease and diabetes mellitus.

LDL size also seems to be an important predictor of cardiovascular events, and progression of coronary artery disease and a predominance of small, dense LDL has been accepted as an emerging cardiovascular risk factor by the National Cholesterol Education Program Adult Treatment Panel III.[1] However, other authors have suggested that LDL subclass measurement does not add independent information to that conferred generically by the LDL concentration along with the other standard risk factors.[8] The number, rather than the density, of LDL particles may be a stronger predictor of CHD.[71]

Therefore, remains debatable whether to measure LDL particle size in cardiovascular risk assessment, and if so, in which categories of patients. In several studies, therapeutical modulation of LDL particle size or number has been of great benefit in reducing the risk of cardiovascular events, but a no clear causal relationship has been shown, due to confounding factors, including lipid and non-lipid variables. Additional studies are needed to investigate the clinical significance of LDL size measurement.

Recently, the Coordinating Committee of the National Cholesterol Education Program stated that very high-risk patients may benefit from more aggressive therapeutic approaches.[186] Screening for the presence of small, dense LDL in patients with coronary or non-coronary forms of atherosclerosis may identify those with even higher vascular risk, and assist in the targeting of appropriate treatment.

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